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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,774	03/13/2003	Tracey Brown	DACO:002US	2305

7590 12/08/2004

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EXAMINER	
BERKO, RETFORD O	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 12/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/088,774	BROWN ET AL.	
	Examiner	Art Unit	
	Retford Berko	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-37 and 39-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-37 and 39-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

James M. Spear
JAMES M. SPEAR
PRIMARY EXAMINER
AU 1615

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement: Applicant's After-Final Amendment and Notice of Appeal filed October 22, 2004 is acknowledged.

Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

Status of Claims

1. The status of the claims is as follows:

(a) Claims 1-12 were cancelled in view of applicant's amendments.

(b) Claims 13-37 and 39-47 are pending following the After-Final amendment.

2. Claims 38 and 48-50 were cancelled

3. **Response to Applicant's Request for Clarification:**

Applicant correctly noted that the Final Office Action mailed May 19, 2004 provided no grounds for the rejections of claims 25-30, 34-37 and 39-47 under 35 USC Sec 103(a). Examiner admits the error that was unintended. Applicant further remarks that the examiner's position is unsupportable as lacking any reasonable basis.

A corrected version of the Office Action is hereby provided for the record with explanation.

Claim Rejections - 35 USC § 112

4. Claims 13-24 remain rejected under 35 USC 112, first paragraph. The scope of the claims is interpreted as preventing metastases of cancer by administering effective amount of hyaluroran. Giving the broadest interpretation to the claims, it is the examiner's position that the claims are directed toward the prevention of cancer from invading a particular area:

(a) The evidence submitted is insufficient and there is no statistical data supporting the prevention of cancer evidenced in the broad scope of the claims. While hyaluloran may be effective in sensitizing non-lymphoid tumor cells to certain antineoplastic agents in vitro and therefore may be useful in treatment of lymphatic cancer, at best such evidence is only a single example of the effectiveness of hyalurolan in cancer treatment and is not supportive of the broad concept of cancer prevention.

(b) Secondly, there is no declaration on file showing evidence of the effectiveness of hyaluoran as effective antineoplastic agent in vivo.

(c) Cancer metastasis invariably involves a complex series of biochemical steps that eventually lead to the re-growth of cancer cells from one site to the other. Simply put, the examiner believes that the following are involved in the process: i.e. tumor invasion is the first step in the complex multi-step process that leads to metastases formation. Following local invasion of adjacent host tissue barriers, the tumor cell must invade the vascular wall or lymphatic channels in order to disseminate. Tumor cells entering the circulation must be able to evade host defenses, survive the mechanical trauma of the blood flow and arrest in the venous or capillary bed of the target organ. Once arrested, the tumor cells must again invade the vascular wall to enter the organ parenchyma. Finally, the extrvasated tumor cell must be able to grow in the "foreign" location different from the tissue of origin in order to initiate a metastatic colony. Simply put, a metastatic tumor cell must possess the capability to traversing all of these indicated steps if not more.

Therefore, based upon this simplified view of metastasis, examiner intepretes the claims and data in examples 2, 4 and Figure 6 as being inadequate to permit broad interpretation that

hyaluloran is effective in the preventing metastasis of cellular proliferation ---the process indirectly involves the prevention of cancer in a subject because as explained, following colonization of a new site, the tumor cell will have to grow.

Claim Rejections-35 USC 102

5. The rejection of claims 13-19, 23-30 and 34-35 under 35 USC 102(b) as being anticipated by both Sakura et al ([Sho 61 (6191986)-17 and Faulk et al (WO 95/30423) is withdrawn in view of applicant's amendment.

Claim Rejections- 35 USC 103

6. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 13-37 and 39-47 remain rejected under 35 USC 103(a) as being unpatentable over Harper et al (US 5, 977, 088) in view of Faulk et al (US 5, 827, 834).

The claims are directed toward a method of preventing metastasis of cellular proliferative disease (e.g. prostate cancer, ovarian, endocrine etc) comprising the step of administering to a subject mammal effective amount of hyaluron (Mol wt of 750, 000-1,500,000 D); wherein the hyaluroran is given in combination with a pharmaceutical carrier or adjuvant (oral, parenteral or topical administration). The claims are also drawn toward administration of chemotherapeutic agent (e.g 5-FU, BCNU or taxane)

Harper et. al. (Patent '088) disclose that effective amounts of pharmaceutical compositions of hyaluronic acid and /or salts, homologues, analogs, derivatives or esters applied to the skin facilitate the transport of medicines and/or therapeutic agents intradermally into the skin to sites of a pathology and/or trauma to sites of trauma (col. 8, lin 60 and col. 9, lin 60), resulting in successful treatment of the disease or condition at the site of trauma or pathology including basal cell carcinoma, metatatic cancer of the breast to the skin and metœstatic melanoma.

Harper neither specifically teach the use of pharmaceutical compositions with hyaluronic acid for elimination of the onset of metastases of cancer cells to other organs nor does it teach the use of hyaluronic acid immediately before or after the drug administration to overcome drug resistance.

Faulk et. al. disclose that administration of a combination of antineoplutic agent mixed with hyaluronic acid to a patient who had advanced carcinoma with metastases—the cases disclosed demonstrate effective use of hyaluronic acid and chemotherapeutic to limit tumor metastases (col 13, lin 60, col 14, lin 20-30, col 15, lin 50-65 col 22, lin 25-45; col 29, lin 25, col 30, lin 30-40 and col 35, lin 1-30). Faulk also disclosed the use of hyaluronic acid either before or after the administration of the antineoplastic agent (col 15, lin 50-65). Faulk alludes to the fact that hyaluronic acid may improve the penetration of the drug through the skin (col 6, lin 60-65).

One of ordinary skill in the art would have been motivated to use a method of administering antineoplastic composition comprising hyalúronic acid and effective agents such as 5-FU to patients in order to obtain inhibition of cell proliferation during treatment of cancer as

was disclosed by Patent '088 (col 23, lin 45-67). It would have been obvious to one of ordinary skill in the art at the time the invention was made to add hyaluronic acid taught in Patent '088 to antineoplastic agent in order to obtain the beneficial effect of the antineoplastic agents taught in Patent '834 because the hyaluronic acid at least is generally known to improve the penetration of drugs into the cell. Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made by the applicant only as far as it pertains to treatment and not prevention of cancer.

Response To Arguments

6. Applicant's arguments filed February 9, 2004 have been fully considered but they are found not persuasive.

7. Applicant argues that specification does indeed support the use of hyaluroran to prevent metastasis (Example 4 and Fig. 6), that mice treated with hyalurolan showed a significant reduction in lymphoid metastasis, as compared to controls.

8. In response to this argument, Example 4 (Spec at page 38) shows the effect of hyalurolan on the in vitro efficacy of –FU to inhibit proliferation of cancer cells. Figure 6 shows the effect of hyaluronan and 5-FU in combination to inhibit metastasis in lymphoid tissue. The evidence is only a single example of the effectiveness of hyalurolan in enhancing the antineoplastic effect and reduction of metastasis and the usefulness for treatment of cancer in lymphoid tissue. However, the evidence is insufficient to support the generic claim—ie the effectiveness of hyalurolan in preventing cancer metastasis. Moreover, the prior art (Sakura et al ([Sho 61 (6191986)-17) discloses the cancer metastasis inhibitory effects of hyalurolan and cross-linked hyalurolan in mice.

9. Applicant argues that Sakura et al does not disclose a method in which metastasis is prevented, that the disclosure at most suggests a method and that the working examples of the reference do not support the methodology. Applicant contends that Sakura et al indicates hyalurolan inhibits binding of cells to tissue, renders the cells anchorage independet and thereby promotes metastasis.

10. In response, Sakura et al discloses that hyaluronic acid reduces bonding ability of tumor cells (page 16) and reduces the number of metastatic foci in lung in murine model (page 19). Applicant's contention of the likelihood that hyalurolan inhibits binding of tumor cells to tissue, rendering the cells anchorage independent and thus likely promoting mestastasis is not disclosed in the prior art reference.

11. Applicant argues that by amending claims 13 and 25 to recite a hyaluronan of molecular weigh 750, 000 daltons which is not taught in the prior art cited, the rejection of the claims under 35 USC 103 over Harper et al (US 5, 977, 088) in view of Faulk et al (US 5, 827, 834) should be withdrawn, that there is no basis for combing the two references as they use hyaluronic acid for different purposes and that the use of hyaluronic acid having molecular weight of less that 750, 000 daltons is inconsistent with the claims that are drawn toward the use of hyaluronic acid of greater molecular weight.

12. In response to this argument, Patent '088 discloses that hyaluronic acid facilitates or causes the transport of medicine and/or therapeutic agent into the skin to the site of pathology and/or trauma (col 9, lin 60-65), providing the motivation to combine hyalurolan with other therapeutic agents in order to effect treatment due to increased bioavailability of drug to sites.

Also, because the prior art discloses the use of hyaluronic acid in the composition, the burden shifts on applicant to show that molecular weight of the compound as claimed is critical.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Retford Berko** whose telephone number is571-272-0590. The examiner can normally be reached on M-F from 8.00 am to 5.30 pm

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Thurman K Page**, can be reached on 571-272-0602.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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